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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,434	11/26/2003	Pingyu Zhong	26050-709.501	8676

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,434	ZHONG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *13-27 and 29-32* is/are withdrawn from consideration.

5)☒ Claim(s) *28 and 33-35* is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/20/04; 6/16/04; 7/21/05; 9/24/05; 3/27/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. In response to the examiners election/restriction mailed on 05/03/2006, the applicants added new claims 33-35, which comprise 3 specific SEQ IDs for VI and 7 specific SEQ IDs for Vh.

Upon further consideration, in view of the newly added claims, the restriction between the antibody pairs as recited in claim 33 (SEQ ID NO:26 and 88; SEQ ID NO:26 and 90; SEQ ID NO:26 and 91; SEQ ID NO:26 and 106; SEQ ID NO:26 and 107; SEQ ID NO:26 and 108; SEQ ID NO:26 and 109; SEQ ID NO:28 and 88; SEQ ID NO:28 and 90; SEQ ID NO:28 and 91; SEQ ID NO:28 and 106; SEQ ID NO:28 and 107; SEQ ID NO:28 and 108; SEQ ID NO:28 and 109; SEQ ID NO:36 and 88; SEQ ID NO:36 and 90; SEQ ID NO:36and 91; SEQ ID NO:36 and 106; SEQ ID NO:36 and 107; SEQ ID NO:36 and 108; and SEQ ID NO:36 and 109) is withdrawn.

However, the restriction between all the other groups (i.e. the SEQ IDs) as encompassed by the restriction/election mailed on 05/30/2006 is maintained.

2. Claims 13-27 and 29-32 are withdrawn from further consideration under 37 C.F.R. 1.142(b) as being drawn to nonelected inventions.

3. Claims 1-12, 29 and 33-35 read on the elected invention and are under examination.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Specifically, please see page 66, line 23. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a monoclonal antibody that specifically binds to a human VEGF with Kd equal to or lower than 0.1 nM, 0.08nM, 0.05 nM, 0.01 nM and 0.005 nM. However, the specification provides insufficient guidance and objective evidence that any monoclonal antibodies that specifically bind to VEGF would predictably have such low dissociation constants. The specification provides no guidance on the administration of the claimed complex or any portion thereof in vivo or in vitro.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In the instant case, the specification discloses a very high number of antibody species (page 15-29 of the specification) with a combination of different heavy and light chains and states that the Kd of selected anti-VEGF antibodies is optionally lower than 100nM ..... optionally lower than 0.005nM (page 16, in particular). However, the specification fails to enable the monoclonal antibodies that are specific to VEGF with a Kd equal to or lower than 0.1 nM, 0.08nM, 0.05 nM, 0.01 nM and 0.005 nM. The specification does not specify any antibody species that correspond to the specific Kd values as claimed. A mere statement within the specification in regard to the range of Kd values of an the antibody does not satisfy the enablement requirements; especially due the unpredictability in the art that exists in the antibody-antigen binding affinity due to the point mutations within the frame work regions or CDRs of the antibody.

For example, Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979) teach that even minor changes in the amino acid sequences of the heavy and light variable regions, in addition to the CDRs, may dramatically affect antigen-binding function as evidenced. Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Further, Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

In addition, Schier et al (J. Mol Biol. 1996, 263:551-567) teach an isolation of picomolar affinity anti-c-erb-2 single chain Fv by molecular evolution of the complementary determining regions in the center of the antibody binding site (title in particular); and indicate that such low Kd values are due to the stringent selection conditions used and the techniques used to monitor selection and screen for higher affinity (page 560 2nd column, in particular). Schier et al teach that when designing a mutant phage antibody library mutations can be randomly introduced, however such

process yields large increases in affinity for hapten antigens, but results with protein binding antibody fragments have been more modest (page 560 1st column, in particular). Further, Schier et al describe the complexity in selecting the residues for mutagenesis analysis to obtain a higher binding affinity (pages 560-562: Design of mutant antibody libraries). Schier et al also teach that a modeling of antigen-antibody should be performed to identify structural residues to be conserved, and residues with solvent accessible side-chains, which would be mutated for an appropriate mutagenesis scanning in order to achieve best results in assessing for increases in binding affinities of an antibody. Thus, Schier et al suggest that in order to construct, produce and evaluate an antibody for a dissociation constants as low as the instantly claimed, the mutations within the CDRs of the antibody have to be specific and; thus the examiner concludes the instantly claimed invention, due to the lack of such information in the specification, would require an undue experimentation.

Thus, the above cited prior art demonstrates that amino acid substitutions which may or may not appear to be an inconsequential chemical modification, will often dramatically affect the biological activity thus affecting the binding affinity and dissociation constant of the antibody. Further, the specification provides no direction or guidance regarding how to produce the antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, at the time the application was filed it would not have been predictable

for of skill in the art to use the pharmaceutical compositions or vaccine formulations as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 7-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Baca et al (WO 98/45331, International Publication Date: 10/15/1998; IDS – 03/27/2006).

The instant claims are drawn to a monoclonal antibody that specifically binds to a human VEGF with Kd equal to or lower than 0.2 nM, wherein the antibody is in a form of scFv, Eab, fully assembled antibody, wherein the Kd is measured at about 4^0C, 25^0C, 37^0C or 42^0C.

Baca et al teach humanized and variant anti-VEGF antibodies that have strong binding affinities for VEGF, inhibit VEGF-induced proliferation of endothelial cells *in vitro* and inhibit tumor growth *in vivo* (abstract, in particular). Baca et al teach that the

antibody includes monoclonal antibodies (page 11 lines 22-25, in particular). Baca et al also teach binding analysis of the VEGF-binding affinities of Fab fragments wherein the variant Y0238-3 was found to have a Kd of less than or equal to 0.2 nM; and another variant Y0313-1 which was found to have a Kd of less than or equal to 0.15 nM, when measured at 25^0C (please see lines 13-16 on page 76 and Table 15, in particular). Further, Baca et al teach that the binding affinities of the antibodies can also be measured at 37^0C as stated on page 72 (table 12, in particular). Baca et al also teach (page 5 first paragraph, in particular) that the anti-VEGF antibody can be a full length antibody (e.g. having an intact human Fc region) or an antibody fragment (e.g. a Fab, Fab', $F(ab')_2$. Baca et al further teach that both variants Y0238-3 and Y0313-1 showed more potent inhibition of VEGF activity than the parent clone (page 77 lines 25-30, in particular).

Thus, Baca et al anticipate the instant claims because Baca et al teach anti-VEGF antibodies, which include monoclonal antibodies, that have a Kd of equal or lower than 0.2nM wherein the Kd can be measured at 25^0C and 37^0C.

Hence, the instant claims are anticipated by Baca et al under 102(b).

Conclusion

9. Claims 28 and 33-35 are found allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER